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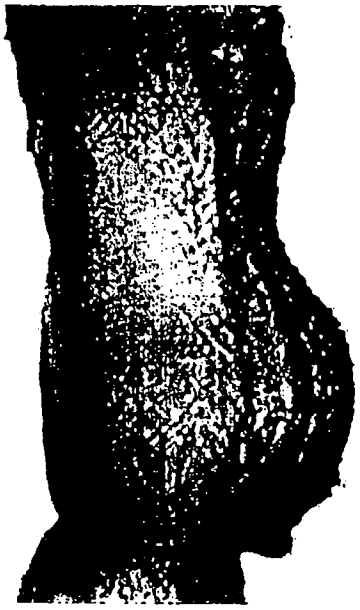

(57) Abstract

A variety of new ways can be used for associating antimicrobial elemental metal with a medical article. The associated antimicrobial metal reduces the risk of infection associated with the medical use of the medical article. New medical articles are produced by some of these new approaches. Some of the methods involve ways of adjusting the dissociation rate of associated elemental metal such that desired degrees of antimicrobial activity can be achieved over selected periods of time.

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MEDICAL ARTICLE WITH ADHERED ANTIMICROBIAL METAL

FIELD OF THE INVENTION

The invention relates to medical articles having elemental metal and/or metal compounds associated with biocompatible material, where the elemental metal or metal composition is effective as an antimicrobial agent. The invention also relates to processes for associating the elemental metal or metal compound with the medical article.

BACKGROUND OF THE INVENTION

A variety of medical articles are designed particularly for contact with a patient's bodily fluids. The duration of this contact may be relatively short, as is typical with wound dressings, or may be long term, as is typical with prosthetic heart valves implanted into the body of a recipient. Some articles such as catheters can have either short term or relatively long term contact. Other articles typically having relatively short term contact with the patient include, without limitation, burn dressings and contact lenses. Other articles typically having long term contact with a patient include, without limitation, implanted prostheses.

Contact of articles with bodily fluids creates a risk of infection. This risk can be very serious and even life threatening. In addition, considerable costs, and longer or additional hospital stays may result due to infection. For example, infections associated with dressings can increase the seriousness of the injury for burn victims. Also, infection associated with an implanted prosthesis can necessitate replacement of the device.

Infections are a particularly common complication resulting from the use in hospitals of percutaneous devices such as catheters. Infections related to catheter use can result from intracutaneous invasion during catheter insertion or from invasion by way of the exit site during use. Adherence of bacteria to the catheter surface complicates treatment of the infection.

Prostheses, i.e., prosthetic articles, are used to repair or replace damaged or diseased organs, tissues and other structures in humans and animals. Prostheses generally must be biocompatible since they are typically implanted for extended periods of time. Examples of prostheses include, without limitation, prosthetic hearts, prosthetic heart valves, ligament repair materials, vessel repair and replacement materials, stents, and surgical patches. A variety of prostheses may incorporate tissue as at least a component of the prosthesis.

Physicians use a variety of prostheses to correct problems associated with the cardiovascular system, especially the heart. For example, the ability to replace or repair diseased heart valves with prosthetic devices has provided surgeons with a method of treating heart valve deficiencies due to disease and congenital defects. A typical procedure involves removal of the native valve and surgical replacement with a mechanical or bioprosthetic valve. Another technique uses an annuloplasty ring to provide structural support to the natural annulus of the native valve.

Prosthetic Valve Endocarditis (PVE) is an infection that can be associated with a heart valve prosthesis. Bacteria can form colonies at the surgical

site associated with the implant and in the fabric of the sewing cuff of the valve prosthesis. The deposition of proteins onto the sewing cuff material also is associated with the attachment of bacteria and other pathogens. For this reason, heart valve recipients are cautioned regarding activities that may introduce bacteria into the bloodstream, such as dental work. For bioprosthetic replacement valves, PVE also is associated with the leaflet portion of the valve as well as the sewing cuff portion of the valve.

PVE can be caused by gram-negative bacteria, gram-positive bacteria, fungi or yeast. PVE caused by gram-positive bacteria is particularly prevalent. Diagnosis is based generally on two positive blood cultures for the same organism along with compatible clinical symptoms. Certain organisms are difficult to culture, however, which can complicate diagnosis.

With respect to replacement heart valves, care must be taken to ensure sterility during production and to prevent contamination during the replacement valve implantation process. For example, to ensure sterility or to reduce perioperative contamination, some surgeons apply antibiotics to the prosthesis prior to implantation. These techniques, however, have relatively short-term effectiveness. In spite of these efforts, PVE occurs in about 2 percent to 6 percent of patients.

Typically, infections occurring within the first 60 days after valve replacement are termed early onset PVE while infections occurring more than 60 days after valve implantation are termed late onset PVE. Mortality rates for early onset PVE may range from 30 percent to 80 percent. Mortality rates for late onset PVE can be greater than 20 percent. These high mortality rates emphasize the seriousness of these

infections. Similar infections are associated with other prostheses.

SUMMARY OF THE INVENTION

Improved procedures involve associating antimicrobial elemental metal and/or metal compounds with a medical article. The antimicrobial elemental metal or metal compound generally is associated with biocompatible material that can contact bodily fluids in use. In particular, antimicrobial elemental metal can be placed within a tissue specimen. Several approaches are described for depositing elemental metal and/or metal compounds in contact with the biocompatible material to inhibit infection at potential locations for microbial colonization. A combination of metals and/or metal compounds can be effectively used to provide short term inhibition of infection along with continuing antimicrobial activity for extended periods of time.

In a first aspect, the invention features a medical article including tissue, the tissue including a deposit of at least about 0.01 mg of antimicrobial elemental metal per gram of tissue. The medical article can be a heart valve prosthesis. The tissue can be crosslinked tissue or uncrosslinked tissue. The tissue preferably includes a deposit of at least about 0.5 mg of elemental silver per gram of tissue.

The tissue can further include a deposit of an antimicrobial metal compound, the metal compound having a solubility in water of less than about 0.01 moles per liter. In some embodiments, the metal compound is disposed within the tissue in regions effectively inaccessible to light. The tissue preferably includes a deposit of at least about 0.5 mg of metal compound per gram of tissue.

In another aspect, the invention features a method including distributing a medical article of the invention for use under the supervision of a health care professional.

In another aspect, the invention features a method of modifying tissue comprising the step of depositing antimicrobial elemental metal on and within the tissue. If the tissue is crosslinked with a multifunctional aldehyde, the depositing step can involve contacting crosslinked tissue with Ag^+ ions. In some embodiments, the deposition of antimicrobial elemental metal includes the steps of:

contacting the tissue in a solution of dissolved metal cations with a precipitation agent to form a metal compound precipitate, the metal compound precipitate being sensitive to reduction by light; and

exposing the tissue, following the precipitation of the metal compound, to light to reduce the metal compound to elemental metal.

The metal cations can be silver cations, where the precipitation agent is selected from the group consisting of Cl^-, Br^-, I^-, alkyl halides, PO_4^{-3}, and CO_3^{-2}.

In other embodiments, the depositing step includes placing the tissue in a solution of metal ions; and applying a voltage to the tissue to deposit elemental metal in contact with the tissue. Preferably, at least about 0.05 mg of silver metal is deposited per gram of tissue.

In another aspect, the invention features a medical article including biocompatible material, the

biocompatible material including a deposit of at least about 0.01 mg of elemental silver per gram of biocompatible material, and at least about 0.01 mg of corresponding metal compound per gram of biocompatible material at a location effectively isolated from exposure to light. The elemental metal can be elemental silver and the corresponding metal compound can be a silver halide.

In another aspect, the invention features a method of producing a medical article including a biocompatible material, the method comprising the step of adding a precipitation agent to the biocompatible material in contact with a solution of metal ions to deposit a first antimicrobial metal compound on and within the biocompatible material. The biocompatible material can include fabric and/or tissue. The metal compound can include a metal constituent that is selected from the group consisting of compounds of Ag, Au, Pt, Pd, Ir, Cu, Sn, Sb, Bi, Zn and combinations thereof. The metal compound preferably has a solubility in water of less than about 0.01 moles per liter. The method can further include the step of adding a second precipitation agent to deposit a second antimicrobial metal compound on and within the biocompatible material. The second antimicrobial compound preferably has a solubility in water of at least about five time greater than the solubility in water of the first antimicrobial compound.

Moreover, the invention pertains to a method for preparing a medical article comprising biocompatible material, the method comprising:

combining a metal composition and the biocompatible material with a solution under reducing conditions, where the

reducing conditions induce a reaction that results in deposition of antimicrobial metal in association with the biocompatible material.

In another aspect, the invention pertains to a method for preparing a medical article comprising biocompatible material, the method comprising:

combining a chemical reducing agent, a metal composition and the biocompatible material in a solution, where the chemical reducing agent induces a reaction that results in the deposition of antimicrobial metal in association with the biocompatible material.

In a further aspect, the invention pertains to a method for preparing a medical article, the method comprising:

illuminating a solution comprising an antimicrobial metal composition, the solution being in contact with biocompatible material, where the illumination results in the deposition of elemental antimicrobial metal, the antimicrobial metal being associated with the biocompatible material.

In addition, the invention pertains to a method for forming a medical article including a biocompatible material associated with an antimicrobial elemental metal, the method comprising:

electroplating an antimicrobial elemental metal onto the biocompatible material.

Furthermore, the invention pertains to a medical article comprising:

a material associated with an antimicrobial elemental metal, the material being

selected from the group consisting of polymers and ceramics.

In another aspect, the invention pertains to a method of producing a medical article, the method comprising physically associating antimicrobial metal with another material in the formation of a biocompatible material. The physical association can be performed by forming, such as by weaving or knitting, thread, yarn or fibers into a fabric. Alternatively, the physical association can be performed by associating a metal leaf onto a biocompatible material. The fabric can comprise silver wire in some embodiments. In some embodiments, the physical association is performed by combining an antimicrobial metal composition with a polymer.

Moreover, the invention pertains to a medical article comprising fabric, the fabric comprising threads, fibers or yarns associated with a first antimicrobial metal and threads, fibers or yarns associated with a second elemental metal interspersed with the threads, fibers or yarns associated with the first antimicrobial elemental metal, where the second elemental metal alters the dissociation rate of the antimicrobial elemental metal when the fabric contacts an aqueous solution.

Furthermore, the invention pertains to a method for forming a medical article, the method comprising:

incorporating a fabric into the medical device, the fabric including thread, yarn, filaments or fibers having an associated antimicrobial elemental metal.

The invention also pertains to a medical article including fabric with associated antimicrobial elemental metal, the fabric having physical alterations to increase the surface area of the antimicrobial elemental metal.

In another aspect, the invention pertains to a method for forming a medical article, the method comprising:

depositing an antimicrobial elemental metal in association with a biocompatible material to form an amorphous deposit of elemental metal.

Moreover, the invention pertains to a medical article comprising:

a biocompatible material having an associated antimicrobial elemental metal and a second elemental metal in electrochemical contact with the antimicrobial elemental metal where the second elemental metal is selected to yield a desired dissociation rate for the antimicrobial elemental metal when the biocompatible material is in contact with bodily fluids.

In addition, the invention pertains to a method for forming a medical article, the method comprising:

associating a biocompatible material with a plurality of elemental metals, the plurality of elemental metals including antimicrobial elemental metal and a second elemental metal in electrochemical contact with the antimicrobial elemental metal where the

second elemental metal is selected to yield a desired dissociation rate for the antimicrobial elemental metal when the biocompatible material is in contact with bodily fluids.

In another aspect, the invention pertains to a method for preparing a medical article, the method comprising:

contacting the medical article in vitro with an oxidizing agent, the medical device comprising an antimicrobial elemental metal.

Furthermore, the invention pertains to a method for producing a medical device, the method including:

reducing a metal compound associated with a biocompatible material to form an elemental metal associated with the biocompatible material.

In another aspect, the invention pertains to a prosthesis having a surface entirely associated with silver.

Other features and advantages of the invention will be apparent from the following detailed description of the invention and the claims.

Brief Description of the Drawings

Fig. 1 is a top view of tissue with deposited elemental silver on a plate with an active culture of S. epidermidis.

Fig. 2 is a top view of control tissue on a plate with an active culture of S. epidermidis.

Fig. 3 is a cross section of heart valve leaflet tissue with deposited AgCl and with H & E stain,

the surface portion of the tissue having been reduced with light to elemental silver.

Fig. 4 is a top view of tissue on a plate with an active culture of B. subtilis, the tissue having deposited AgCl and elemental silver produced by reduction with light while in a salt solution.

Fig. 5 is a top view of tissue on a plate with an active culture of S. epidermidis, the tissue having deposited AgCl and elemental silver produced by reduction with light while in a saline solution.

Fig. 6 is a top view of tissue on a plate with an active culture of B. subtilis, the tissue having deposited AgCl and elemental silver produced by reduction by light while in a formalin solution.

Fig. 7 is a top view of tissue on a plate with an active culture of S. epidermidis, the tissue having deposited AgCl and elemental silver produced by reduction by light while in a formalin solution.

Fig. 8 is a top view of control tissue on a plate with an active culture of B. subtilis.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

New approaches are described to associate antimicrobial metal and/or metal compounds with medical articles that contact bodily fluids. In particular, tissue components of medical articles can be provided with adhered elemental metal and/or metal compounds. The association of antimicrobial elemental metal and/or metal compounds with the medical articles inhibits the microbial colonization of the article. Suitable antimicrobial metals include, for example, Ag, Au, Pt, Pd, Ir, Cu, Sn, Sb, Pb, Bi, Zn and combinations thereof. The effectiveness of antimicrobial elemental metals is thought to be due to the slow formation of corresponding metal ions. Approaches are described for adjusting the

dissociation or ionization rate of the antimicrobial metal to achieve a desired degree of antimicrobial effectiveness.

A variety of medical articles can be used to contact bodily fluids of a patient. Relevant biocompatible medical articles generally incorporate a biocompatible material which is intended to contact the patient's biological fluids and/or tissues. Bodily fluids include, for example, blood, plasma, serum, interstitial fluids, saliva and urine. The patient can be an animal, especially a mammal, and preferably is a human.

The antimicrobial metal can be associated with a portion or all of the surface of the medical device. In particular, a prosthesis, such as a heart valve, valved grafts, vascular grafts, pacemaker, defibrillator, lead, or annuloplasty ring, can be formed with essentially the entire surface directly associated with an antimicrobial elemental metal, such as silver (Ag). Alternatively, selected partial or localized portions of the prosthesis surface can be directly associated with the antimicrobial metal. For example, pivot guards and/or outer diameter of a heart valve prosthesis can be associated with the metal. In some embodiments, only parts of the prosthesis that contact tissue are associated with antimicrobial metal. The heart valve prosthesis can be a mechanical heart valve prosthesis or a tissue based heart valve prosthesis, a biosynthetic heart valve or a combination thereof.

Improved methods for associating antimicrobial elemental metals and/or metal compounds with medical articles generally involve directly depositing antimicrobial metals on and within tissue and/or other biocompatible materials. With respect to antimicrobial

metal compounds, the compound can be deposited by adding a precipitation agent to the biocompatible material while the biocompatible material is incubating in a soluble metal solution. The antimicrobial metal compound that is precipitated generally must be relatively insoluble in water or other appropriate solvent. The precipitation agent causes a relatively insoluble metal compound to come out of solution into and onto the tissue or other biocompatible material.

In addition to, or as an alternative to metal compound deposition, elemental metal can be deposited. Using traditional methods, a substrate receiving a coating of elemental silver must withstand harsh, vacuum conditions generally used in the deposition of the silver metal. Tissue, in particular, generally cannot withstand these harsh conditions.

Several approaches are described for associating antimicrobial metal with tissue and/or other biocompatible materials. A first approach involves the reaction of metal solutions with a chemical reductant, such as unreacted crosslinking agent, which may be present in or added to the biocompatible material. A second approach involves photoreduction of metal compounds in the presence of a biocompatible material. Also, elemental metal can be deposited onto materials by electroplating. In addition, threads or the like coated with antimicrobial metal can be woven, knit or otherwise formed into fabric to achieve a higher surface area relative to fabric coated directly with antimicrobial metal.

Multiple elemental metals can be codeposited in electrical contact such that the ionization of the antimicrobial elemental metal is altered by the presence of the other metal. Thus, the ionization rate can be

adjusted to a more desirable value using codeposition of metals. Alternatively, the ionization rate can be altered by treating the surface of the deposited metal. In particular, the surface of the deposited metal can be oxidized.

The formation of antimicrobial elemental metal on biocompatible material, such as tissue, can provide relatively long term protection from infection as well as directed protection for shorter periods. Long term protection is especially important for the function of prostheses and the like which remain in contact with a patient's bodily fluids for an extended period of time. Furthermore, the use of deposits of selected metal compounds can be used to design the article with a rate of antimicrobial metal release appropriate for the particular article. An appropriate release rate can be selected based on the length of time that the article generally contacts bodily fluids. A combination of deposited antimicrobial agents can be more effective than a single antimicrobial agent.

While reducing the risk from infection, the patient's plasma levels of the corresponding metal ions should stay safely below toxic levels. Healthy humans generally have, for example, plasma levels of Ag of about 0.2 μg/l to about 10 μg/l, where 10 μg/l corresponds to about 0.01 ppm or 10 ppb. In the blood, silver ions are carried by high molecular weight proteins, such as glutathione and transferrin. Silver cations are removed from the body with about 90 percent being excreted in bile and significant amounts being excreted in urine. Plasma levels of silver in sheep resulting from implantation of silver coated polyester have been evaluated. In these studies serum silver levels are well below the lowest reported levels causing

toxic effects. See, K. S. Tweden et al., J. of Heart Valve Disease, 6:553-561 (1997).

Serum silver ion concentrations of about 300 ppb have been associated with toxic symptoms including argyria in gingiva and cheeks, nephrotic syndrome and leukopenia. Silver ion concentrations of about 40 μmol/l (about 4 mg/l) are known to cause rapid cell death. Therefore, it is preferable to keep silver and other metal ion concentrations in the blood stream safely below toxic levels and preferably below levels where any symptoms are observable.

A. Biocompatible Article

Relevant biocompatible devices or articles include all medical articles that contact bodily fluids. These articles can be organized roughly into three groups: implanted (implantable) devices, percutaneous devices and cutaneous devices. Implanted devices broadly include articles that are fully implanted in a patient, i.e., are completely internal. Percutaneous devices include items that penetrate the skin, thereby extending from outside the body into the body. Cutaneous devices are used superficially, for example, at a wound site or at a moist membrane.

Implanted devices include, without limitation, cardiovascular prostheses and other types of prostheses such as pacemakers, pacing leads, defibrillators, transplant organs such as artificial hearts, ventricular assist devices, anatomical reconstruction prostheses such as breast implants, heart valve prostheses, cardiovascular repair patches such as pericardial patches, coronary stents, vascular grafts or conduits, biological conduits, pledgets, sutures, annuloplasty rings, stents, staples, valved grafts, vascular grafts, orthopedic spinal implants, maxillofaical reconstruction

plating, dental implants, intraocular lenses, clips, sternal wires, bone, skin, ligaments, tendons, and combinations thereof. Percutaneous devices include, without limitation, catheters of various types, cannulas, drainage tubes such as chest tubes, surgical instruments such as forceps, retractors, needles, and gloves, and catheter cuffs. Catheters can be used for accessing various bodily systems such as the vascular system, the gastrointestinal tract, or the urinary system. Cutaneous devices include, without limitation, skin grafts, burn dressings, wound dressings of all types, and contact lenses. These biocompatible articles can be made from the biocompatible materials described below.

B. Biocompatible Material

Appropriate biocompatible materials include natural materials, synthetic materials and combinations thereof. Natural, i.e., biological, material for use in the invention includes relatively intact (cellular) tissue as well as decellularized tissue. These tissues may be obtained from, for example, natural heart valves; portions of natural heart valves such as roots, walls and leaflets; pericardial tissues such as pericardial patches; connective tissues; fascia; bypass grafts; tendons; ligaments; skin patches; blood vessels; cartilage; dura matter; skin; bone; umbilical tissues; and the like.

Natural tissues are derived from a particular animal species, typically mammalian, such as human, bovine, porcine, seal or kangaroo. These natural tissues generally include collagen-containing material. Natural tissue is typically, but not necessarily, soft tissue. Appropriate tissues also include tissue equivalents such as tissue-engineered material involving

a cell-repopulated matrix, which can be formed from a polymer or from a decellularized natural tissue. Tissue materials are particularly useful for the formation of tissue heart valve prostheses.

Tissues can be fixed by crosslinking. This provides mechanical stabilization, for example, by preventing enzymatic degradation of the tissue. Glutaraldehyde is typically used for fixation, but other difunctional aldehydes or epoxides can be used. Tissues can be used in either crosslinked or uncrosslinked form, depending on the type of tissue, the use and other factors.

Relevant synthetic materials include, for example, polymers, metals and ceramics. Appropriate ceramics include, without limitation, hydroxyapatite, alumina and pyrolytic carbon. Appropriate metals include medals or alloys approved for medical use including, for example, steel and titanium. Appropriate synthetic materials include hydrogels and other synthetic materials that cannot withstand severe dehydration.

Polymeric materials can be fabricated from synthetic polymers as well as purified biological polymers. The polymeric materials can be woven into a mesh to form a matrix or substrate. Alternatively, the synthetic polymer materials can be molded or cast into appropriate forms.

Appropriate synthetic polymers include, without limitation, polyamides (e.g., nylon), polyesters, polystyrenes, polyacrylates, vinyl polymers (e.g., polyethylene, polytetrafluoroethylene, polypropylene and polyvinyl chloride), polycarbonates, polyurethanes, poly dimethyl siloxanes, cellulose acetates, polymethyl methacrylates, ethylene vinyl

acetates, polysulfones, nitrocelluloses and similar copolymers. Conductive polymers include, for example, doped polymers of poly(sulfur nitride), polyacetylene, poly(p-phenylene), poly(phenylene sulfide) and polypyrrole. Other suitable polymers include resorbable polymers such as dextran, hydroethyl starch, gelatin, derivatives of gelatin, polyvinylpyrrolidone, polyvinylalcohol, poly[N-(2-hydroxylpropyl) methacrylamide], polyglycols, polyesters, poly (orthoesters), poly(ester amides), polyanhydrides. Resorbable polyesters include, for example, poly (hydroxy acids) and copolymers thereof, poly(ϵ-caprolactone), poly (dimethyl glycolic acid), and poly (hydroxy butyrate). Preferred resorbable polymers include, for example, D, L-polylactic acid, L-polylactic acid, poly(glycolic acid), and copolymers of L-lactic acid, D-lactic acid and glycolic acid.

Biological polymers can be naturally occurring or produced *in vitro* by, for example, fermentation and the like. Purified biological polymers can be appropriately formed into a substrate by techniques such as weaving, knitting, casting, molding, extrusion, cellular alignment and magnetic alignment. For a description of magnetic alignments see, for example, R. T. Tranquillo et al., Biomaterials 17:349-357 (1996). Suitable biological polymers include, without limitation, collagen, elastin, silk, keratin, gelatin, polyamino acids, cat gut sutures, polysaccharides (e.g., cellulose and starch) and copolymers thereof.

Biocompatible materials can include a combination of the various natural materials and synthetic materials described above. For example, some prosthesis are made entirely from tissue, or tissue with fabric, such as sewing rings, or metal components.

Other relevant prostheses are made completely from metal, ceramics or a combination of metal, ceramics and, optionally, additional natural or synthetic materials. Mechanical heart valves, artificial hearts, ventricular assist devices, coronary stents, annuloplasty rings, conducting leads and defibrillators are relevant products, which generally are made from metallic, polymeric and/or ceramic components.

C. Deposited Metal Compounds

The deposition of metal compounds into a biocompatible material involves the formation of insoluble precipitants involving antimicrobial metal ions. Suitable antimicrobial metal ions include, for example, ions of Ag, Au, Pt, Pd, Ir, Cu, Sn, Sb, Bi, Zn and combinations thereof. The biocompatible material first is incubated in a solution of a soluble metal composition. A precipitation agent is added to the incubating biocompatible material such that an insoluble metal compound precipitates from solution forming a deposit of the insoluble compound generally on or in portions of the biocompatible material contacting the solution.

The soluble metal salt compositions may be unstable due to decomposition in light. It may be desirable to keep the soluble salt solutions in the dark as well as initially incubating the biocompatible material with the soluble salt solutions in the dark.

Preferred metal compositions include silver compositions. For example, the biocompatible material can be incubated with silver nitrate. Then, a chloride salt, such as sodium chloride, can be added to precipitate silver chloride. Similarly, a bromide salt, such as sodium bromide, can be used to precipitate silver bromide, which is about an order of magnitude

less soluble than silver chloride. A variety of other salts can be used to precipitate silver including, for example, I^{-1}, CO_3^{-2} and PO_4^{-3}. Organic precipitation agents can also be used. For example, organic halides that react by way of an S_N1 nucleophilic substitution can form precipitates of silver halide. Suitable organic halides generally include tertiary alkyl halides, allylic halides and benzylic halides.

Other compounds similarly can be precipitated based on other antimicrobial metals. For example, biocompatible material can be incubated with soluble cupric nitrate or cupric sulfate. Then, for example, stearic acid or diammonium hydrogen phosphate, $(NH_4)_2HPO_4$, can be added to the solution to precipitate cupric stearate or cupric phosphate, respectively. Similarly, the biocompatible material can be incubated with water soluble zinc compounds such as zinc chloride or zinc nitrate. Suitable precipitation agents include, for example, phosphates and stearic acid. Palladium diacetate can be precipitated from palladium chloride by the addition of acetic acid or a salt of acetic acid. Similar precipitations can be performed with other antimicrobial metal compounds based on relative insolubility of the compound.

For some metals, the precipitation agent can act by reducing the metal to a less soluble cation. For example, cupric ions (Cu^{+2}) are reduced by aldehydes to form cuprous ions (Cu^{+1}). A traditional reagent for this reaction is cupric tartrate ($CuC_4O_6H_4$), "Fehling's solution." Generally, insoluble CuO is formed. The aldehyde can be supplied by way of an unreacted crosslinking agent bound to the biocompatible material or as a separately added reagent.

The precipitated antimicrobial metal compound is selected based on the desired antimicrobial activity. This may involve a balance of several different factors. A significant factor is sufficient dissolution of the metal composition such that a desired amount of antimicrobial effectiveness is reached. At the same time, the precipitated compound should not dissolve too rapidly so that the antimicrobial effectiveness is too short lived or that toxic levels of metal are reached. A mixture of relatively insoluble salts can be used effectively to form a desired antimicrobial activity, as described further below.

The rate of dissolution of a metal compound is influenced by the solubility of the metal compound as well as kinetic factors. The rate of dissolution generally depends on the conditions in which the biocompatible material is placed. Typically, the biocompatible material is not kept at equilibrium conditions since fluid generally flows over the biocompatible material such that antimicrobial metal ions are removed. Therefore, the rate at which the metal ions are removed depends on the particular use.

Generally, suitable metal compounds have a solubility in water of less than about 0.01 moles/liter, preferably less than about 0.001 moles/liter, and for more long term applications less than about 0.0001 moles/liter. For use in prostheses that can benefit from antimicrobial activity over several years, even less soluble metal compositions can be used effectively. Similarly, less soluble metal compositions would be suitable for use with biocompatible materials that are subject to continuous fluid flow. Information regarding the kinetics of dissolution in water generally is known but is not systematically quantified. Empirical

evaluations can be performed to determine the rate that the metal ions are removed in particular applications.

The quantity of precipitated metal compound generally is selected to yield, to the extent possible, a suitable amount of antimicrobial activity for a desired length of time. The amount of deposited metal compound should not interfere significantly with important mechanical properties of the biocompatible material. If the conditions for depositing the metal salt are relatively harsh, it may be desirable to limit the exposure time while accepting a corresponding decrease in deposited metal compound. The amount of antimicrobial metal compound generally is greater than about 0.01 mg per gram of dry biocompatible material, and preferably from about 0.05 mg to about 40 mg per gram of dry biocompatible material, and more preferably from about 0.1 mg to about 20 mg/gram of dry biocompatible material.

D. Deposited Antimicrobial Metal

Elemental metal can be deposited as an alternative to or in addition to depositing metal compounds. The approaches for applying deposits of antimicrobial metal can be broadly classified according to whether the deposition takes place from a vapor phase, a solid phase or from a liquid phase. Antimicrobial metals include, for example, silver, gold, platinum, palladium, iridium, copper, tin, lead, antimony, bismuth and zinc. Certain types of deposition approaches may be especially suitable to associate antimicrobial metal with particular types of corresponding biocompatible materials. Four particular approaches are described for the preparation of biocompatible materials that have a deposit of antimicrobial elemental metal for use in the

biocompatible article. The first three approaches are solution based methods to treat finished medical devices, subassemblies or components of medical devices. The fourth method can use either a solution based method, a solid phase method or a vapor phase method to prepare components that are physically associated to form the material, such as weaving thread or the like into a fabric.

To determine the amount of metal to deposit, the rate of dissolution can be taken into consideration. The environment in which the biocompatible material is placed can influence the rate of dissolution. Given a particular rate of dissolution, the amount of deposited metal establishes the length of time over which metal is available for microbial inhibition. Processing considerations such as time, cost and deposition limitations may influence the amount of metal deposited. Toxicity issues also may dictate the deposition of lesser amounts of elemental metal.

Some of the procedures described herein involve contacting the biocompatible material with a metal salt solution at some point during the processing. Some metal ions generally associate themselves with the biocompatible material during this contact. This additional form of treatment is a natural part of the relevant procedures described herein. Thus, the extent of reduction can be varied to alter the amount of ionic species immediately available relative to the amount of reduced antimicrobial metal available over time.

With any method of deposition, the amount of deposited metal should not interfere significantly with important functionality of the biocompatible material. The amount of antimicrobial elemental metal, such as silver, incorporated into the medical article generally

is greater than about 0.01 mg per gram of dry biocompatible material, and preferably greater than about 0.05 mg per gram of dry biocompatible material, and more preferably from about 0.1 mg to about 20 mg per gram of dry biocompatible material. Alternatively, the proportion of antimicrobial metal could be higher if significant portions of the medical article are fabricated from the antimicrobial metal. When incorporated into a medical article, the proportion of elemental metal relative to the total quantity of biocompatible materials can be less than the above range since portions of the biocompatible materials may not have deposits of elemental metal. The amount of metal deposited on the biocompatible material can be influenced by the harshness of the conditions used to deposit the elemental metal. For example, for some materials exposure to solutions with pH values significantly deviating from physiological values should be minimized.

In general, the biocompatible material can be subjected to deposition of elemental metal prior to, during or after processing into a biocompatible article. For example, to form a bioprosthetic or mechanical heart valve with a fabric component, the tissue or mechanical component and the fabric can be separately subjected to deposition of antimicrobial elemental metal using conditions suitable for each material. Similarly, only the tissue or mechanical components or only the fabric can be subjected to antimicrobial metal deposition. Following the desired deposition of antimicrobial metal, the tissue/mechanical component and the fabric component can be combined. Alternatively, the tissue/mechanical component and the fabric component can be formed into a biocompatible article followed by the deposition of

antimicrobial elemental metal using a suitable method for the different materials.

1. Chemical Reduction

In this approach, the biocompatible material is contacted with a solution including an antimicrobial metal composition. The metal compound generally is relatively soluble in the solvent being used. Suitable silver compounds include, for example, silver nitrate. Generally, the solution is relative concentrates such that the process proceeds at a reasonable rate. A reducing agent is then added to the solution. The corresponding metal is then deposited upon reduction onto the biocompatible material, as an elemental metal or as a less soluble metal compound.

The solvent is selected such that the biocompatible material is not degraded by the solvent. Suitable solvents are generally aqueous although other solvents, such as alcohols, can be used. The metal compound should be sufficiently soluble such that the concentration of metal compound in solution provides a desirable level of elemental metal deposition upon exposure to the reducing agent.

Suitable reducing agents include, for example, aldehydes, sodium borohydride, H_2 and CO for reduction of a variety of metals. Gaseous reducing agents can be bubbled through the solution. In particular, aldehydes are known to reduce silver ions to elemental silver. The traditional silver compound for the reduction with aldehydes is ammoniacal silver hydroxide ($Ag(NH_3)_2OH$), "Tollen's reagent." Aldehydes can be supplied as partly unreacted multifunctional aldehyde compounds, such as crosslinking agents. Similarly, a palladium chloride solution can be reduced to form palladium metal using hydrogen or carbon monoxide (CO), which can be bubbled

into the solution. Elemental copper can be precipitated from copper solutions by the addition of aluminum, iron or zinc particles.

Generally, the reduction process produces elemental metal in association with the substrate. Alternatively, the reduction converts the metal to a less soluble cation. Then, a metal compound precipitates onto the substrate. For example, cupric ions (Cu^{+2}) are reduced by aldehydes to form cuprous ions (Cu^{+1}). A traditional reagent for this reaction is cupric tartarate ($CuC_4O_6H_4$), "Fehling's solution." Generally, insoluble CuO is formed.

When processing tissue, it is preferred to keep the pH between values of about 4 and about 11 more preferably between about 6 and about 8.5, and even more preferably between about 7.0 and about 8.0, to the extent that the pH can be adjusted within the particular processing approach. The solution can include a buffer with a pH in a desirable range. Suitable buffers can be based on, for example, the following compounds: phosphate, borate, bicarbonate, carbonate, EDTA acetate, cacodylate, citrate, and other organic buffers such as tris(hydroxymethyl)amino methane (TRIS), N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), and morpholine propanesulphonic acid (MOPS). Some buffers may be unsuitable for use with certain metal solutions. Ionic strength can be adjusted, if desired, by the addition of inert salts, the identity of which generally depends on the nature of the deposition process and the corresponding compositions.

2. Photochemical Deposition

Many silver compounds are subject to photochemical reduction. To perform the photochemical deposition, a sufficiently soluble silver compound is

dissolved in a solvent. Suitable solvents are inert with respect to the biocompatible material. Suitable silver compounds include, for example, silver nitrate. The biocompatible material is placed in the solution and exposed to either natural or artificial light to reduce the metal compound to elemental silver. The elemental silver is deposited on the biocompatible materials, which can act as a nucleation site. Suitable solvents and buffers are as described above. In alternative embodiments, a metal first can be deposited in contact with the biocompatible material as a relatively insoluble metal compound that is then subjected to light.

3. Electrochemical Deposition

To achieve electrochemical deposition, the biocompatible material must be rendered electrically conducting. Thus, if the material is not inherently electrically conducting, the material can be surface treated with graphite or the like to render the material electrically conducting. Biocompatible materials of particular interest include, as a component, polymers, ceramics and other metals such as titanium, cobalt, alloys thereof and Elgiloy®, a cobalt-chromium-nickel-molybdenum-iron alloy. A variety of suitable polymers (natural and synthetic) are described above.

Electrochemical deposition involves the application of a voltage in order to electroplate elemental metal in contact with the biocompatible material. The biocompatible material functions as a cathode. The voltage required depends on the counter reaction and the concentrations of ions in solution. Selection of the metal composition influences the effectiveness of the plating process. Silver plating works effectively with $[Ag(CN)_2]^{-1}$ present in solution.

The electroplating generally is performed with an aqueous solution of a water soluble compound of the desired metal. In particular, electrochemical deposition can involve the application of a voltage to tissue in order to electroplate, from the metal solution, elemental metal in contact with the tissue.

4. Physical Association

In an embodiment of a solid phase method, elemental metal can be associated with a biocompatible material by direct physical association of the metal with the material. For example, a metal leaf can be pressed onto the biocompatible material. Alternatively, wire made from antimicrobial metal can be woven into the material, such as a fabric, or sewn through the material, such as a tissue. In a further alternative embodiment, increasing proportions of the medical device can be fabricated from antimicrobial metal, up to and including the full device.

Similarly, an antimicrobial metal composition and/or elemental metal can be mixed with a polymer during formation. Multiple compounds and/or elemental metals can be mixed together to achieve a desired amount of effectiveness. The polymer can be formed into thread or into sheets of material for formation into a medical article or a component or subassembly. The antimicrobial metal can leach from the polymer during use. In particular, an antimicrobial elemental metal composition can be mixed with a hydrogel, such as a partially sulfonated hydrogel or a hydrogel with an appropriate counter ion or ligand that would reversibly bind the appropriate metal, that is applied as a coating to the biocompatible material, such as a fabric.

Metal coated fabric can be produced by deposition of metal onto the fabric. A higher surface

area per weight of elemental metal can be obtained by coating the threads, yarn, filaments or fibers prior to forming the fabric. In other words, the fabric is woven, knitted or otherwise formed from metal coated thread, yarn, filament, fiber or the like. The metal can be deposited in the form of elemental metal and/or as a metal composition.

The fabric made from the metal coated threads maintains the porous nature of the fabric. The tightness of the weave determines the degree of porosity. The porosity may be advantageous for certain applications, in particular where tissue ingrowth is desirable. For example, the fabric can be used to form a sewing ring for a medical device, such as a heart valve prosthesis. The threads can be woven, knitted or otherwise formed into fabric using a variety of processes including conventional processes.

The metal can be deposited on the thread using either vapor or solution based methods. The solution based methods described above, for example, can be used. Vapor phase methods include, for example, vapor deposition, metal plasma deposition, sputtering and magnetron sputtering. Vapor phase deposition techniques generally require varying degrees of vacuum, i.e., low pressure.

Vapor deposition can simply involve directing vaporized metal toward the substrate to be metalized. Vapor deposition preferably is performed using ion-beam-assisted deposition (IBAD) under high vacuum as described, for example, in U.S. Patent 5,474,797 to Sioshansi et al., incorporated herein by reference, although other vapor deposition techniques are within the invention. IBAD involves an evaporator that forms a vapor of the desired metal. The metal vapor is

delivered to the substrate by a beam of ions formed from one or more gases.

E. Combination of Approaches

With implanted heart valve prostheses, the two month period immediately following implantation is a particularly significant period with respect to the prevention of infection since the greatest number of cases of PVE typically occur in this time period. Nevertheless, the risk of infection due to prosthesis implantation continues for a year or more. It may be possible to improve the overall effectiveness of antimicrobial treatments by combining two or more antimicrobial agents. For example, it may be desirable to combine one deposited compound having relatively high metal ion loss rate over the first two to three month period with another antimicrobial agent that provides continued antimicrobial effectiveness for a year or more. An additional compound can be deposited that provides an especially large amount of antimicrobial ions during the first days or weeks from the implantation. Additional or alternative combinations of antimicrobial agents can be used, as desired.

There are a variety of ways of combining the methods herein. Two or more different metal compounds with different solubility constants can be precipitated onto the biocompatible material to provide two sources of antimicrobial metal ions with different dissolving rates. For example, silver bromide has a solubility less than a tenth the solubility of silver chloride. Therefore, a combination of silver chloride and silver bromide can result in an extended time of antimicrobial effectiveness relative to silver chloride alone and greater short term effectiveness than silver bromide alone. In a preferred embodiment, a second

antimicrobial metal compound would have a solubility in water of at least five times greater than the solubility in water of a first antimicrobial metal compound. Generally, the compounds can be deposited sequentially or simultaneously by the concurrent addition of two or more precipitation agents.

Multiple elemental metals can be deposited such that the different elemental metals are or are not in electrical contact with each other. The oxidation potential of one metal may influence the rate of oxidation of the other metal. In this way, the rate of oxidation of one metal can be accelerated or slowed by the selection of a second metal. An additional metal can also be selected also to supply beneficial effects. In particular, an additional elemental metal can itself be an antimicrobial elemental metal, such as the combination of silver and copper. Alternatively, an additional elemental metal can be an anticalcific elemental metal. Anticalcific metals include, for example, aluminum, iron, manganese, zinc, gallium, lanthanum and beryllium.

If multiple elemental metals are in electrical contact, one metal generally is stabilized in its elemental form while the oxidation of the other metal is enhanced. In other words, the less easily oxidized metal is generally preserved by the preferential oxidation of the other metal until the more easily oxidized metal is consumed or no longer in electrical contact with the more stable metal. Thus, the stabilized metal may not be as effective at imparting beneficial effects while the other metal is present. After the more easily oxidized metal is consumed, the more stabilized metal is oxidized to impart the desired effect. For example, a combination of silver and copper

deposits would result in the faster ionization of copper and the slower ionization of silver.

Even if the elemental metals are not in direct physical contact, the presence of a second elemental metal may influence the oxidation rate and corresponding effectiveness of the first elemental metal as an antimicrobial agent and vice versa. This influence is the result of the local presence of ions and atoms of the other metal.

If one or more antimicrobial elemental metals are in electrochemical contact (electrical contact and/or chemical contact) with one or more other metals, the additional other metal(s) can introduce another activity and/or can adjust the delivery rate of the antimicrobial elemental metal(s).

For vapor phase techniques, the deposition of multiple metals can be performed sequentially or simultaneously. Specifically, multiple metals can be placed in successive layers, the metals can be deposited simultaneously to create an amorphous surface, and/or the metals can be patterned onto the substrate such that each metal contacts a selected portion of the substrate. In addition, different elemental metals can be incorporated onto different portions of one or more sections of biocompatible material for incorporation as components into a single medical article.

Generally, solution-based methods involve the sequential deposition of the elemental metals. Solution phase techniques can be used to pattern a single portion of biocompatible material if some effort is applied to contact only the desired portion with the solution. The solution can be applied, for example, by dipping, spraying or submerging the biocompatible material. The order of deposition may be influenced by the method or

methods used to deposit the elemental metals if, for example, one elemental metal is unstable during the deposition of the second metal. The placement of the multiple metals generally is influenced by the impact on the antimicrobial effectiveness resulting from the particular relationship between the metals, as described above.

Alternatively, metal compounds with antimicrobial activity can be deposited along with an antimicrobial elemental metal. These metal compounds can be deposited by precipitation of the compound from a solution of a corresponding soluble metal compound by the addition of a precipitation agent, generally an appropriate anion or a reducing agent to form a lower oxidation state metal ion. A particularly preferred combination is elemental silver combined with a silver compound such as silver chloride. This combination is described in the Examples below. The silver metal results from the light induced reduction of the silver chloride to silver metal at the portion of tissue that is susceptible to light. The elemental metal and metal compound can be selected to provide effectiveness over different time periods. Additional metal and/or metal compounds can be included to incorporate more than two different antimicrobial agents.

With any of the methods involving multiple antimicrobial agents, the agents should be deposited such that the device maintains adequate mechanical properties. For example, heart valve prostheses have components that must flex during use. In addition, different parts of the biocompatible material can be associated with distinct antimicrobial agents, either metal compounds or elemental metal, to ensure adequate mechanical properties of the prosthesis. Similarly,

whether one or more antimicrobial agents are deposited, only a portion or certain parts of the biocompatible material may be associated with the antimicrobial agents. For example, the entire device can be covered with one antimicrobial agent while only select portions are covered with a second antimicrobial agent. Further, portions of the device could have one or more antimicrobial agents, or not be covered at all.

Furthermore, the procedures described herein can be combined with other approaches to reduce microbial infection. For example, glutaraldehyde treatment is effective in reducing microbial contamination of medical articles. Glutaraldehyde can be used effectively even if it is not needed as a crosslinking agent. Similarly, immersing a medical article in alcohol or an aqueous alcohol solution can reduce microbial contamination.

Some of the procedures described herein involve contacting the biocompatible material with a metal salt solution. Some metal ions generally associate themselves with functional groups within the biocompatible material. This additional form of treatment is a natural part of the procedures described herein.

Also, commonly assigned U.S. Patent Application Ser. No. 08/787,139 to Tweden et al., entitled "Medical Article with Adhered Antimicrobial Metal Ions and Related Methods," incorporated herein by reference, discloses a method of associating antimicrobial metal cations with exogenous storage structures, for example, metal storage proteins such as ferritin. Exogenous storage structures are not native or inherent to the biocompatible material. The exogenous storage structures containing antimicrobial

ions are then bound to biocompatible material. The procedures based on exogenous storage structures can be combined with the procedures described herein for depositing elemental metal and/or insoluble metal compounds in association with biocompatible material. The association of the exogenous storage structures with the biocompatible material can be performed before, during or after deposition of metal and/or metal compounds into or onto the biocompatible material.

F. Control of Ionization Through Surface Treatment

The surface of the metal deposits can be subjected to oxidizing conditions to enhance the dissolution of the antimicrobial elemental metal. Oxidation is a necessary step to the solubilization of the metal as a metal compound or metal ion. In particular, with antimicrobial elemental metals, it may be desirable to have an enhanced antimicrobial impact during the initial use of the biocompatible article as a result of the oxidized surface of the metal. Long term antimicrobial effectiveness results from the remaining elemental metal. The degree of oxidation can be adjusted to yield the desired degree of dissolution of the elemental metal.

The oxidizing conditions can be supplied by a chemical oxidizing agent or by a physical treatment. Suitable chemical oxidizing agents include, for example, hydrogen peroxide, super oxides, oxygen radicals, ozone, hydrogen sulfide, permanganate, Grignard reagents, metal ions with suitable redox potentials, sulfur and nitric acid. The chemical oxidizing agents can be supplied in an aqueous or nonaqueous solution.

Suitable physical oxidation treatments include, for example, flame treatment. With flame

treatment, the biocompatible material with the elemental metal deposits are passed near a flame. The materials should not pass too close to the flame since the flame could damage the biocompatible material. On the other hand, the materials should not pass too far from the flame or the flame may be ineffective at oxidizing the elemental metal. In the presence of methane or hydrogen, contact with the flame can be reducing. Thus, a metal compound deposited on a substrate can be converted partially or totally to elemental metal by reduction caused by the flame.

Alternatively, a biocompatible material such as a fabric with associated antimicrobial metal can be subjected to mechanical treatment to increase the dissociation rate. For example, the biocompatible material can be cut to increase the surface area. The cuts can be made in a variety of ways as long as the mechanical durability of the biocompatible material is not compromised. Similarly, the biocompatible material can be mechanically abraded or scored such that the surface becomes rough, thereby increasing the surface area.

G. Processing Considerations

In general, the biocompatible material can be subjected to elemental metal or metal compound deposition prior to, during or following processing into a biocompatible article. For example, a heart valve prosthesis can be treated to deposit antimicrobial metal either before or after attachment of a sewing cuff. The mechanical properties of the biocompatible material, especially tissue, should not be significantly degraded by the antimicrobial metal deposition. In particular, material properties such as flexural modulus, stress and strain responses and mechanical strength should not

deteriorate significantly, and the material preferably maintains its flexibility.

There are certain situations where multiple biological activities are desirable. In these situations, materials can be made by forming a bioactive coating on a base material, where the bioactive coating can include, for example, cell adhesion molecules, such as fibronectin or other arginine-glycine-aspartic acid sequence containing peptides, anticoagulants such as heparin and hirudin, growth factors, chemotactants, and combinations thereof.

Articles with bioactive coatings then can be subjected to further application of antimicrobial elemental metal using the techniques described herein. In some cases, the order of the application of the antimicrobial metal and the other bioactive material can be reversed. If appropriate, the application of the antimicrobial metal and other bioactive material can be performed simultaneously. Performance may be influenced by the order of application of the different active agents, and in such cases, the order of application can be selected based on performance considerations. Empirical evaluation of these factors can be performed, if desired.

H. Combination with Anticalcification Agents

Polyvalent metal cations such as Fe^{+3} and Al^{+3} have been shown to be useful in reducing calcification that is associated with implanted prostheses. As described above, anticalcification elemental metals can be codeposited with antimicrobial elemental metals. The anticalcification elemental metal can be a source of anticalcific cations. The elemental metals can be deposited in such a way that both the antimicrobial metal and the anticalcific metal are effective over

relevant time periods required for antimicrobial effectiveness and anticalcific effectiveness. Furthermore, the antimicrobial metal and anticalcific metal can be deposited on different portions of the prosthesis that are particularly sensitive to each effect.

In addition, exogenous storage structures have been shown to be useful in delivering these polyvalent cations. See, commonly assigned and copending U.S. Patent application 08/690,661 to Schroeder et al., entitled Calcification-Resistant Biomaterials," incorporated herein by reference. These exogenous storage structures with stored anticalcific ions can be combined with the deposits of antimicrobial elemental metal.

Alternatively, compositions including these polyvalent metal cations can be deposited into the biocompatible material along with the antimicrobial metal or metal composition. For example, aluminum palmitate can be precipitated from a solution of aluminum chloride by the addition of palmitic acid.

I. Storage, Packaging, Distribution and Use

Following deposition of desired antimicrobial agents, the biocompatible material, possibly formed into a medical article, is stored. The biocompatible material or device is stored under appropriate environmental conditions for the particular material or device without compromising the efficacy of the anitmicrobial treatment. Preferred storage techniques minimize the risk of microbial contamination.

Still, due consideration should be given to possible loss over time of the deposited antimicrobial metal during storage. If excessive amounts of antimicrobial agent would be lost or absorbed into the

storage environment, the storage time should be selected such that the amount of antimicrobial metal lost from the biocompatible material is within a satisfactory level. Additives can be added to the storage solution to reduce the loss of antimicrobial metal, such as silver nitrate if silver compounds are deposited in the biocompatible material, or antioxidants, such as ascorbic acid.

For distribution, the medical articles are placed in sealed and sterile containers. The containers are generally dated such that the date reflects the maximum advisable storage time accounting for possible degradation of the antimicrobial agents as well as other factors. The containers are packaged along with instructions for the proper use and/or implantation of the medical device and along with appropriate and/or required labeling. The containers are distributed to health care professionals for use in appropriate medical procedures such as implantation of a prosthesis and the like.

The reduction of infection frequency is an important objective in the design of medical devices that contact bodily fluids. The methods disclosed herein expand the design options available to achieve this objective. In particular, the approaches described above are particularly advantageous for the processing of certain biocompatible materials and for the design of improved antimicrobial effectiveness over desired time frames. The antimicrobial metals associated with the substrates should inhibit microbial attachment, growth, and/or colonization. Furthermore, these antimicrobial approaches provide for additional flexibility with respect to combinations with anticalcification agents. Antimicrobial metals have been shown to provide broad

spectrum effectivity, are relatively cost effective with respect to antibiotics, and have demonstrated lower incdence of resistant strain development.

EXAMPLES

In the following examples, the silver nitrate was ACS reagent grade 99+% pure, distributed by Aldrich Chemical Co., Milwaukee, WI. Purified water used was purified by reverse osmosis and had a resistivity of 10 megaohms per cm or greater. The photographs in Figs. 1-8 are at a magnification from about 4x to about 6x, except for Fig.3 which has a magnification of about 40x.

Example 1 - Aldehyde Reduction

Tissue samples were glutaraldehyde-crosslinked, porcine aortic tissue. To prepare a solution for each tissue sample, a 10.0 ml quantity of 5 percent weight/volume silver nitrate and a 5.0 ml quantity of 10 percent sodium hydroxide was placed into a glass test tube. A gray precipitate of silver oxide resulted. Then, a 2.5 ml quantity of 2.8 percent aqueous ammonium hydroxide (ammonia) solution was added to the test tube. The tube was stoppered and shaken. Additional quantities totaling 3.0 ml of ammonium hydroxide solution were added to the tube, and the tube was shaken until almost all of precipitate was dissolved. In total, 5.5 ml of ammonium hydroxide were added to each tube. The resulting solution in the tube had a pH of 11.6.

The 5 percent weight per volume silver nitrate solution was prepared by mixing 5 grams of silver nitrate with sufficient pure water to fill a 100 ml volumetric flask. Following standard notation in the field, the sodium hydroxide solution was prepared by 1 to 5 volume dilution with purified water of a 50 percent by weight NaOH solution from CSM Chempure, Houston,

Texas. Similarly, the 2.8 percent ammonia solution was prepared by 1 to 10 volume dilution with purified water of a 28 percent by weight ammonia solution from Mallinckrodt, Paris, Kentucky.

Glutaraldehyde treated aortic valve leaflets and 8 mm aortic wall biopsy punches were each placed in separate test tubes that were prepared with ammoniacal silver hydroxide as described in the last paragraph. Equivalent tissue samples were not placed in the test tubes for use as controls. The cardiac tissues were received from an FDA approved abattoir. To prepare the tissues, the tissues were cleaned of fat and rinsed in 0.9 percent saline (Baxter, Deerfield, IL) overnight to remove blood and other debris. The tissue samples were placed in a 0.5 percent HEPES buffered, glutaraldehyde solution. The samples were incubated in this solution for approximately one month. The 0.5 percent HEPES buffered, glutaraldehyde solution was prepared by placing 3.86 g NaCl (Fisher Scientific, Springfield, New Jersey), 11.92 g HEPES buffer (Sigma Chemical Co., St. Louis, MO), and 10 ml 50 percent by weight glutaraldehyde solution (EM Science, Ft. Washington, PA) in a 1.0 liter volumetric flask along with sufficient pure water to file the flask to the one liter mark.

A 10 ml quantity of 5 percent by weight formaldehyde solution was added to the tube to plate out the silver. The 5 percent formaldehyde solution was prepared by mixing 1.35 ml of 37 percent formaldehyde solution (Sigma Chemical Co., St. Louis, MO) with sufficient pure water to fill a 10 ml volumetric flask. The tissue was incubated for a total of 30 seconds. The relatively short incubation time was selected to minimize any detrimental effect on the tissue from the alkaline pH. Following removal from the ammoniacal

silver hydroxide solutions, the tissue samples were rinsed and soaked sequentially in three 50 ml quantities of purified water for 5 min., 2 hours and 24 hours, respectively. The silver deposited tissue samples did not appear mechanically degraded or less flexible than untreated control samples.

A portion of the samples were sent for histological examination. Following rinsing, the remaining silver deposited tissue samples were placed on plates with active cultures of Staphylococcus epidermidis, Bacillus subtilis, or Escherichia coli bacteria. Staphylococcus epidermidis is the most common etiological agent for early PVE. Generally, one tissue sample was placed on each plate. The tissue samples demonstrated very good antimicrobial properties after 24 hours of incubation as demonstrated by a region free from bacterial growth ringing the tissue samples, as shown in Fig. 1. Control samples of the same glutaraldehyde treated tissue without the silver treatment were infected with the bacterial cultures, as shown in Fig. 2.

Example 2 - Salt Precipitation and Reduction

A 10.0 ml quantity of 5 percent aqueous silver nitrate solution, as described in Example 1, was placed in a glass test tube. Tissue samples included glutaraldehyde-crosslinked, porcine aortic leaflets, porcine aortic wall and bovine pericardium. The tissue samples were prepared as described in Example 1. The tissue samples were separately incubated in tubes containing the silver nitrate. Silver nitrate is thought to be relatively benign with respect to tissue, and dilute silver nitrate has been used for topical applications, for example, for eyes, mouth ulcers, and irrigation of the bladder and urethra.

Following the 30 minute incubation, the samples were removed from the silver nitrate and placed in 50 ml of a 0.9 percent by weight aqueous saline (NaCl) solution (Baxter, Chicago, IL.) to precipitate out the silver as AgCl. The saline was replaced after five minutes and again after another 15 minutes. Half of the samples were kept in the saline and exposed to light for about one week to reduce the exposed silver compounds to silver metal. Silver deposits were visible on the tissue within five hours of incubation. The other half of the silver treated samples were removed from the saline and placed in 10 percent formalin (formaldehyde and ethanol) from Fisher Chemical, Fairlawn, New Jersey. The samples in formalin similarly were exposed to light to reduce silver salt to silver metal.

The tissue samples reduced in the saline solution were brownish in color while the tissue samples reduced in the formalin were gray in color. The tissue samples did not appear mechanically degraded or less flexible than control samples. Referring to Fig. 3, cross sections of the leaflets reveal that elemental silver was localized in a band of tissue near the surface. The inner portions of the tissue had deposits of silver chloride. Presumably, sufficient light does not penetrate to the inner portions of the tissue to reduce significant quantities of the silver chloride to elemental silver.

Leaflet samples from both the saline containing tubes and the formalin containing tubes were placed on plates with active cultures of Bacillus subtilis bacteria and Staphylococcus epidermidis bacteria. Referring to Figs. 4-7, the tissue samples demonstrated very good antimicrobial properties as

demonstrated by a region free from bacterial cultures ringing the tissue samples. Control samples of the same glutaraldehyde treated tissue without the silver treatment were infected with the bacterial cultures, as shown in Figs. 2 and 8.

Example 3 - Implantation Studies

Nine samples were implanted into rats to evaluate the rate of silver loss from the tissue. Two samples were porcine aortic leaflets prepared according to Example 1 above. Two samples were 8 mm root punches from a porcine aortic wall prepared according to Example 1 above. Five samples were 8 mm punches from bovine pericardium prepared according to Example 2 above, with reduction performed in formalin. Samples from the same tissue specimens were retained for pre-implant evaluation. The nine samples were placed subcutaneously in the back of juvenile male rats using color coded suture. The samples were removed 21 days after implantation. Following removal, the samples were placed in 0.9% saline prior to analysis. Each tissue sample was removed from the saline and sectioned in half. One half portion of each tissue sample was cleaned of host tissue and used for elemental analysis. The second half portion of each tissue was placed in 10 % formalin and stored for histological examination.

The amounts of silver in the tissue samples before and after implantation are presented in Table 1. Silver quantities were measured using an ICP-AES (Inductively Coupled Plasma- Atomic Emission Spectroscopy) instrument, an Atom Scan 16™ by Thermo Jarrell Ash Corp., Franklin, MA.

TABLE 1

Type of Tissue	Pre-implant (Ag mg/g of dry tissue)	Post implant (Ag mg/g of dry tissue)
Ex. 1 Porcine Aortic Leaflet	2.26±0.53	2.00±0.47*
Ex. 1 Porcine Aortic Wall	2.42±0.67	2.08±0.86*
Ex. 2 Bovine Pericardium	5.63±0.72	5.25±0.83

It can be seen that the quantity of silver deposited according to the procedure of Example 2 was about twice the quantity of silver deposited by the procedure of Example 1.

The embodiments described above are intended to be exemplary and not limiting. Other embodiments may be within the scope of the claims. Although the present invention has been described with reference to preferred embodiments, workers skilled in the art will recognize that changes may be made in form and detail without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A medical article comprising tissue, said tissue comprising a deposit of at least about 0.01 mg of antimicrobial elemental metal per gram of tissue.

2. The medical article of claim 1, wherein said medical article comprises a heart valve prosthesis.

3. The medical article of claim 1, wherein said tissue comprises crosslinked tissue.

4. The medical article of claim 1, wherein said tissue comprises uncrosslinked tissue.

5. The medical article of claim 1, wherein said tissue comprises a deposit of at least about 0.5 mg of elemental silver per gram of tissue.

6. The medical article of claim 1, wherein said tissue further comprises a deposit of an antimicrobial metal compound, said metal compound having a solubility in water of less than about 0.01 moles per liter.

7. The medical article of claim 6, wherein said metal compound is disposed within said tissue in regions effectively inaccessible to light.

8. A method comprising distributing a medical article of claim 1 for use under the supervision of a health care professional.

9. A method of modifying tissue comprising the step of depositing antimicrobial elemental metal on and within said tissue.

10. The method of claim 9, wherein said depositing includes the steps of:

contacting said tissue in a solution of dissolved metal cations with a precipitation agent to form a metal compound precipitate, said metal compound precipitate being sensitive to reduction by light; and

exposing said tissue, following the precipitation of said metal compound, to light to reduce said metal compound to elemental metal.

11. The method of claim 9, wherein said depositing step comprises:

placing said tissue in a solution of metal ions; and

applying a voltage to said tissue to deposit elemental metal.

12. The method of claim 9, wherein at least about 0.01 mg of silver metal is deposited per gram of tissue.

13. A medical article comprising biocompatible material, said biocompatible material comprising a deposit of at least about 0.01 mg of elemental metal per gram of biocompatible material, and at least about 0.01 mg of corresponding metal compound per gram of biocompatible material at a location effectively isolated from exposure to light.

14. The medical article of claim 13, wherein said elemental metal is elemental silver and said corresponding metal compound is a silver halide.

15. A method of producing a medical article comprising a biocompatible material, said method comprising the step of adding a precipitation agent to said biocompatible material in contact with a solution of metal ions to deposit a first antimicrobial metal compound on and within said biocompatible material.

16. The method of claim 15, wherein said biocompatible material comprises fabric.

17. The method of claim 15, wherein said biocompatible material comprises tissue.

18. The method of claim 15, wherein said metal compound has a solubility in water of less than about 0.01 moles per liter.

19. The method of claim 15 further comprising the step of adding a second precipitation agent to deposit a second antimicrobial metal compound on and within said biocompatible material.

20. The method of claim 19, wherein said second antimicrobial compound has a solubility in water of at least about five time greater than the solubility in water of said first antimicrobial compound.

21. A method for preparing a medical article comprising biocompatible material, said method comprising:

combining a metal composition and said biocompatible material with a solution under reducing conditions, where said reducing conditions induce a reaction that results in the deposition of antimicrobial metal in association with said biocompatible material.

22. The method of claim 21 wherein said metal composition comprises a silver composition.

23. The method of claim 21 wherein said metal composition comprises Ag, Au, Pt, Pd, Ir, Cu, Sn, Sb, Pb, Bi, Zn, or combinations thereof.

24. The method of claim 21 wherein said biocompatible material comprises tissue.

25. The method of claim 21 wherein said biocompatible material comprises a polymer.

26. The method of claim 21 wherein said biocompatible material comprises a ceramic.

27. The method of claim 21 wherein said biocompatible material comprises a metal.

28. The method of claim 21 wherein said deposited antimicrobial metal comprises elemental metal.

29. The method of claim 21 wherein said deposited antimicrobial metal comprises a metal compound.

30. The method of claim 21 wherein said biocompatible material comprises thread, fiber or yarn, and said method further comprises weaving said thread, fiber or yarn into a fabric.

31. The method of claim 21 wherein said reducing conditions are produced by the addition of a chemical reducing agent to the solution.

32. The method of claim 31 wherein said chemical reducing agent comprises an aldehyde.

33. The method of claim 21 wherein said reducing conditions are supplied by illuminating the solution, where said illumination results in the deposition of of elemental metal in association with said biocompatible material.

34. The method of claim 33 wherein said elemental metal comprises silver.

35. The method of claim 21 wherein said reducing conditions are supplied by applying a current to the solution with said biocompatible material acting as a cathode.

36. The method of claim 35 wherein the biocompatible material is selected from the group consisting of polymers and ceramics.

37. A method of producing a medical article, the method comprising physically associating antimicrobial metal with another material in the formation of a biocompatible material.

38. The method of claim 37 wherein the physical association is performed by forming a fabric from

threads, yarns or fibers that has associated antimicrobial metal.

39. The method of claim 38 wherein the fabric comprises silver wire.

40. The method of claim 37 wherein the physical association is performed by combining an antimicrobial metal composition with a polymer.

41. The method of claim 37 wherein the physical association is performed by pressing a metal leaf onto the biocompatible material.

42. A method for producing a biocompatible material, the method comprising:

reducing a metal compound associated with a biocompatible material to form an elemental metal associated with the biocompatible material.

43. The method of claim 42 wherein the reduction is performed with a flame.

44. The method of claim 42 wherein the reduction is performed by contacting the biocompatible material with a chemical reducing agent.

45. A heart valve prosthesis having a surface entirely associated with silver metal.

46. A medical article comprising fabric, said fabric comprising threads, fibers or yarns associated with a first antimicrobial metal and threads, fibers or yarns associated with a second elemental metal interspersed with said threads, fibers or yarns associated with said first antimicrobial elemental metal, where said second elemental metal alters the dissociation rate of said antimicrobial elemental metal when said fabric contacts an aqueous solution.

47. The medical article of claim 46 wherein said first antimicrobial elemental metal comprises silver and said second elemental metal comprises aluminum.

48. A medical article comprising fabric with associated antimicrobial elemental metal, said fabric having physical alterations to increase the surface area of said antimicrobial elemental metal.

49. The medical article of claim 48 wherein said physical alterations are selected from the group consisting of cuts, abrasions and scores.

50. A method for forming a medical article, the method comprising:

depositing an antimicrobial elemental metal in association with a biocompatible material to form an amorphous deposit of elemental metal.

51. A medical article comprising:

a biocompatible material having an associated antimicrobial elemental metal and a second elemental metal in electrochemical contact with said antimicrobial elemental metal where said second elemental metal is selected to yield a desired dissociation rate for said antimicrobial elemental metal when said biocompatible material is in contact with bodily fluids.

52. A method for forming a medical article, said method comprising:

associating a biocompatible material with a plurality of elemental metals, said plurality of elemental metals including an antimicrobial elemental metal and a second elemental metal in

electrochemical contact with said antimicrobial elemental metal where said second elemental metal is selected to yield a desired dissociation rate for said antimicrobial elemental metal when said biocompatible material is in contact with bodily fluids.

53. A method for preparing a medical article, said method comprising:

contacting said medical article in vitro with an oxidizing agent, said medical device comprising an antimicrobial metal.

54. The method of claim 53 wherein said oxidizing agent comprises hydrogen peroxide, super oxides, oxygen radicals, hydrogen sulfide, permanganate, Grignard reagents, metal ions with suitable redox potentials, sulfur or nitric acid.

55. The method of claim 53 wherein said oxidizing agent comprises a flame.

Figure 1.

Figure 2.

Figure 3.

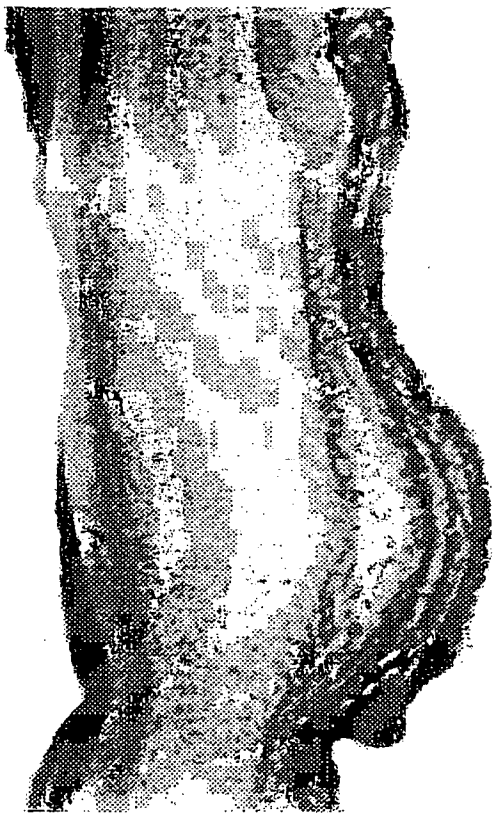

Figure 4.

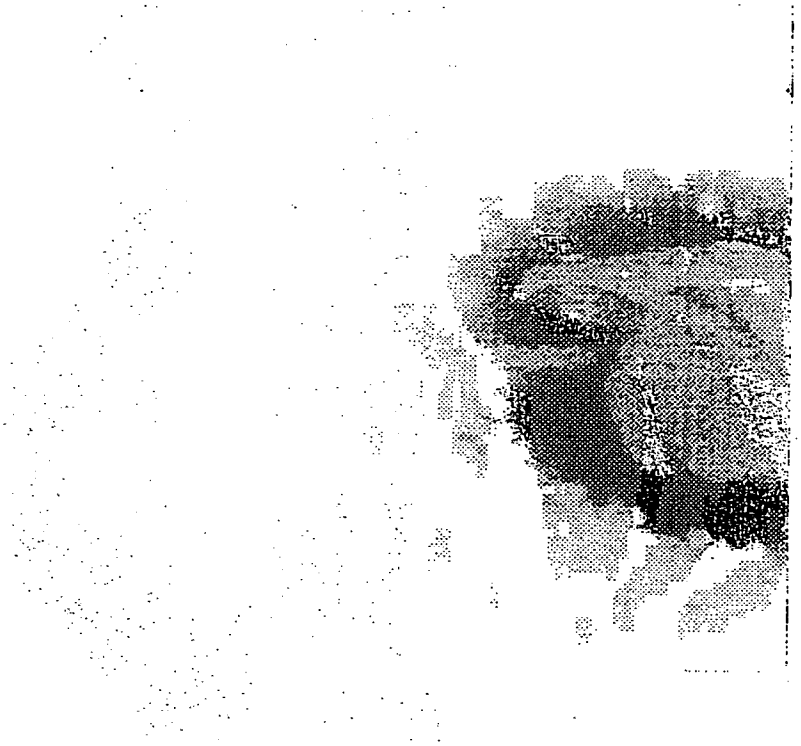

Figure 5.

Figure 6.

Figure 7.

Figure 8.

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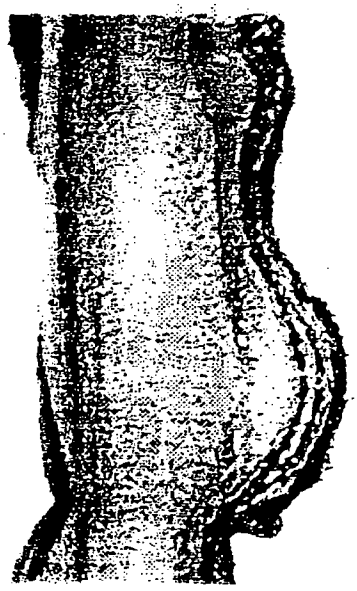

(57) Abstract

A variety of new ways can be used for associating antimicrobial elemental metal with a medical article. The associated antimicrobial metal reduces the risk of infection associated with the medical use of the medical article. New medical articles are produced by some of these new approaches. Some of the methods involve ways of adjusting the dissociation rate of associated elemental metal such that desired degrees of antimicrobial activity can be achieved over selected periods of time.

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INTERNATIONAL SEARCH REPORT

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Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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